Ibd CAncer and seRious infections in Europe

I-CARE

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BACKGROUND

Inflammatory bowel disease (IBD), encompassing Crohn's Disease (CD) and ulcerative Colitis (UC), is a chronic, disabling, incurable condition affecting 3 million Europeans (1). Current therapeutic options are limited and comprise 5ASA, immunosuppressive (IS) and anti-TNF (infliximab, adalimumab, certolizumab pegol, and golimumab) (2). Evolving treatment algorithms and current guidelines result in an earlier and wider use of anti-TNF therapy in IBD patients (3). For instance, up to 40% of CD and 20% of UC patients are currently exposed to anti-TNF at the population level in France.

1. Safety profile of anti-TNF agents alone or in combination with immunosuppressives

Anti-TNF and IS in combination are more effective than anti-TNF alone in both CD and UC. However this strategy may be associated with an excess risk of malignancies, especially lymphoma, and opportunistic infections. Hence, we must urgently address safety concerns for anti-TNF alone or in combination with IS. Several factors can influence the safety profile of anti-TNF therapy such as IBD phenotype, treatment duration as well as disease activity and severity. In the field of IBD, it was demonstrated in the CESAME cohort study that a huge cross-sectional observational cohort is able to address accurately and rapidly the long-term major safety issues associated with the prolonged use of thiopurines, with an immediate impact on updated guidelines on IBD therapeutic strategies (4, 5). Clinical trials and registries are inadequate to address all these issues. A large statistically powered prospective cross-sectional observational cohort with a standardized follow-up at the European level is eagerly awaited.

2. Efficacy and impact of the natural history of IBD: potential for disease modification of anti-TNF agents

Anti-TNF therapy is associated with greater clinical remission rates and steroid tapering in randomized, controlled trials at one year. IBD is a progressive disease. Achieving and maintaining mucosal healing, prevention of bowel damage and reduction of IBD-related surgeries and hospitalizations have emerged as new therapeutic goals in IBD (6). The potential for disease modification using IS therapy (mainly thiopurines) is questionable, while the impact of anti-TNF on the natural history of IBD (mucosal healing, bowel damage, surgeries, and hospitalisations) beyond one year is unknown. The impact of anti-TNF therapy

on long-term outcomes cannot be accurately studied using available databases (clinical trials and registries). Only real world data coming from a very large cohort of IBD patients with a long-term follow-up, beyond one year, can address this issue. Such cohort studies will also provide unique opportunity to measure the impact of IBD-related medications (5-ASA, immunosuppressant, and anti-TNF) on the risk of malignancies, especially on colorectal cancer.

3. Patient-reported outcomes: capturing the real disease burden of IBD (7-10)

In the EU approximately 3 Million people are affected by IBD. Ninety percent of IBD patients are between 20 and 60 years of age (societies' main work force). IBD cannot be cured and its chronicity affects patients' ability to complete personal, family or socio-professional plans. Hence, IBD is a chronic disabling condition. The Food and Drug Administration (FDA) is moving from the Crohn's Disease Activity Index to patient-reported outcomes (PROs) and objective measures of disease, such as findings from endoscopy. PROs will become an important aspect of assessing activity of inflammatory bowel disease (IBD) and for labeling specific drugs for this disease. PROs always have been considered in the management of patients with rheumatoid arthritis or multiple sclerosis, and have included measurements of quality of life, disability, or fatigue. Several disease-specific scales have been developed to assess these PROs and commonly are used in clinical trials. Outcomes reported by patients in clinical trials of IBD initially focused on quality of life, measured by the Short-Form 36 questionnaire or disease-specific scales such as the Inflammatory Bowel Disease Questionnaire or its shorter version. Recently considered factors include fatigue, depression and anxiety, and work productivity, as measured by the Functional Assessment Chronic Illness Therapy-Fatigue, the Hospital Anxiety Depression, and the Work Productivity Activity Impairment Questionnaire, respectively. Although disability is generally recognized in patients with IBD, it is seldom measured. The international IBD disability index currently is being validated. PROs will be a major primary end point of future trials. Few data are available on how treatment affects PROs in patients with IBD and the evolution of PROs over time has never been investigated in large prospective cohorts. This is a prerequisite to a better assessment of disease burden in IBD and to the development of disease-modifying agents for these patients. The I-CARE project is a great opportunity to study the psychometric properties of PRO questionnaires used in this project, combining both classical test (construct validity using confirmatory factor

analysis) and item response theories (partial credit model, Rasch family model). We could complete the knowledge about the validity of the PRO through the study of the invariance of items (differential items functioning) across countries, sex, disease history, etc. (=bias of measure) (5, 6). The longitudinal design of I-CARE project also provides us the opportunity to better understand and interpret the differences among group of patients studying the "response shift", a phenomenon which can affect standard psychometric properties of PRO questionnaires, such as reliability and validity (7).

4. Risk-benefit of anti-TNF based strategies and healthcare costs

The annual direct healthcare costs for IBD in EU are estimated around 4-5 Billion Euros. Anti-TNF monoclonal antibodies for immune-mediated inflammatory disorders, including IBD, account for the most important drug expense in Western countries. Before earlier and wider use of anti-TNF based strategies can be recommended in order to change patient- and disease-related outcomes, more information on the benefit-risk ratio and cost-effectiveness of long-term anti-TNF use is required(6, 11). One still need to determine whether increased use of anti-TNF agents in IBD is cost-effective. We need to collect real-world data e.g. demographic data and specific patient traits or medical history to refine both the scope and the limits of the clinical benefits of treatment. Comparative cost-of-illness calculations between the different options and their safety will provide ground for decision by Healthcare systems to include the strategy within the best quality of care recommendations for managing IBD. Overall, there is an urgent need to evaluate the benefit-risk ratio and cost-efficacy of current therapeutic strategies in order to optimize the appropriate use and the right place of anti-TNF agents, with the final aim of providing the best quality of care for patients with IBD. Other biologics such as vedolizumab have recently approved for IBD and data on their risk-benefit profile and cost efficacy are also eagerly awaited. Previous or ongoing registries initiated and/or sponsored by pharmaceutical companies cannot accurately address these issues as they are compromised by inherent bias. The CESAME cohort study, enrolling almost 20.000 French patients with IBD, has demonstrated the feasibility of conducting a large prospective cohort study in IBD (4, 5).

I-CARE focus on anti-TNF will be the first prospective study establishing the benefit-risk ratio and cost-efficacy of strategies based on an increasing use of anti-TNF therapy for IBD.

STUDY OBJECTIVES

The **primary objective** of I-CARE is to assess prospectively the presence and the extent of **safety** concerns (**cancers (especially lymphoma) and serious infections risks**) for anti-TNF alone or in combination with thiopurines among IBD patients. Safety profile of all steroids formulation will also be analysed. We will stratify the risk of cancers and serious infections according to IBD phenotype and disease activity (clinical, radiologic and endoscopic).

The **four main secondary objectives** of the I-CARE project are:

- To investigate prospectively the impact of anti-TNF based strategies on the **natural history** of IBD and their **potential for disease modification** by collecting validated surrogate markers such as mucosal healing and disease complications such as bowel damage (strictures, fistulas, abscess), surgeries, and hospitalizations

- To assess the evolution of **PROs** on a yearly basis and the impact of anti-TNF agents on **PROs** in IBD

- To evaluate the **benefit-risk ratio** of strategies based on an earlier and wider use of anti-TNF therapy for IBD

- To assess the **healthcare costs and cost-efficacy** of current therapeutic strategies in IBD.

STUDY DESIGN

This is a European prospective longitudinal observational multicenter cohort study. A total of 16 countries will participate. However, the final list will be confirmed upon confirmation of the country capacity by the National Coordinator: Belgium, Denmark, France, Germany, Hungary, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, and UK. In France, the Investigators will be selected by the National Coordinators (Corinne Gower and Stéphane Nahon) from the members of EPIMAD, ANGH and CREGG, as well as the GETAID.

Study duration: 4 years

- One-year inclusion period
- Three-year follow-up period

Sample size, number of investigators, number of patients per investigator, participating countries

Calculation of sample size was made based on the primary objective of ICARE. We estimated that a minimum of 47,000 patient-years are needed for the study to have a statistical power of 80% to detect a lymphoma hazard ratio of at least 3.5 in the groups of patients receiving thiopurines, either alone or in combination with anti-TNF, relative to patients not receiving thiopurines (i.e. receiving anti-TNF alone or no IS). The final patient population will be up to 17,600 and the follow-up duration for each patient will be 3 years. A total of 800 investigators working in reference centers in IBD will be recruited via ECCO and National Coordinators.

Investigators will be all European gastroenterologists from the participating countries voluntary for participating in the study on an unpaid basis, and accepting to provide phone number and e-mail address for the purpose of the study.

Each investigator will include a total of 22 inpatients or outpatients that he personally manages for IBD, matching the inclusion criteria and stratified according to the exposure to immunosuppressive therapy at inclusion:

- Group 1: **5 patients** who have **never received biological agents or immunosuppressant** (all 5-ASA and steroids formulations are permitted)
- Group 2: **5 patients** receiving thiopurines alone
- Group 3: **5 patients** treated with **anti-TNF therapy alone** without any concomitant immunosuppressant
- Group 4: **5 patients** treated with **anti-TNF therapy in combination with thiopurines or methotrexate**
- Group 5: **2 patients:** For investigators following IBD patients treated with vedolizumab, a 5th Group is constituted with enrollment of **one patient treated with vedolizumab alone** (without any concomitant immunosuppressant) and **one patient treated with vedolizumab in combination with thiopurines or methotrexate.**

STUDY POPULATION

Inclusion criteria:

- Patient with an established diagnosis of Crohn's disease, ulcerative colitis or IBD, unclassified made at least 3 months earlier based on usual radiological, endoscopic or histological criteria.
- Patient 18 and older accepting to sign the informed participating consent form, stating that he accepts to provide personal details (mobile and home phone number, e-mail address), to complete the e-PRO as required and to be contacted by a Study Coordinator and his gastroenterologist for the purpose of the study during the entire study period and during follow up if required.

Exclusion criteria:

- Patient unable to sign the informed consent form
- Patient with no regular access to internet
- Patient refusing to sign the informed consent form
- Treatment at entry in the study with an immunomodulator different from thiopurines and methotrexate (cyclosporine, tacrolimus, mycophenolate mofetil, etc.)
- Patient previously enrolled in a Randomized Clinical Trial *(If the investigational product received was blinded, and if the treatment is unknown at time of enrollment in I-CARE)*

ROLES AND RESPONSIBILITIES

Gastroenterologist investigator

- The gastroenterologist selects and consents the patient and enters the baseline demographic data of the patient in the eCRF. The accuracy of all the information entered by the patient must be validated at least once a year by the gastroenterologist who will complete the e-summary form. She/he will also be requested to evaluate endoscopic and imaging disease activity based on available reports using a predefined and simplified scoring system.

Study Coordinators (SC)

- The accuracy and completeness of the information reported by the patients will be checked on a monthly basis by the Study Coordinators working under the responsibility of the National Coordinators and supported by the GETAID Project Manager. The Study Coordinators will ensure that all data are completed on a monthly basis by the patients and will follow up if required.
- For cancer/dysplasia, all hospitalizations and surgeries, if the patient did not or could not upload the report, SCs will have to get a copy of the corresponding **histological or hospitalization report** from the patient, general practitioner, gastroenterologist or other organ specialist, and upload an anonymized copy on the eCRF portal for review and validation by the Gastroenterologist.
- Occurrence of death within the preceding year: this information will be obtained by the patient circle after failure of direct contact, or by the general practitioner, attending gastroenterologist or other organ specialist. Study Coordinators are requested to get reliable information on the cause of the death.

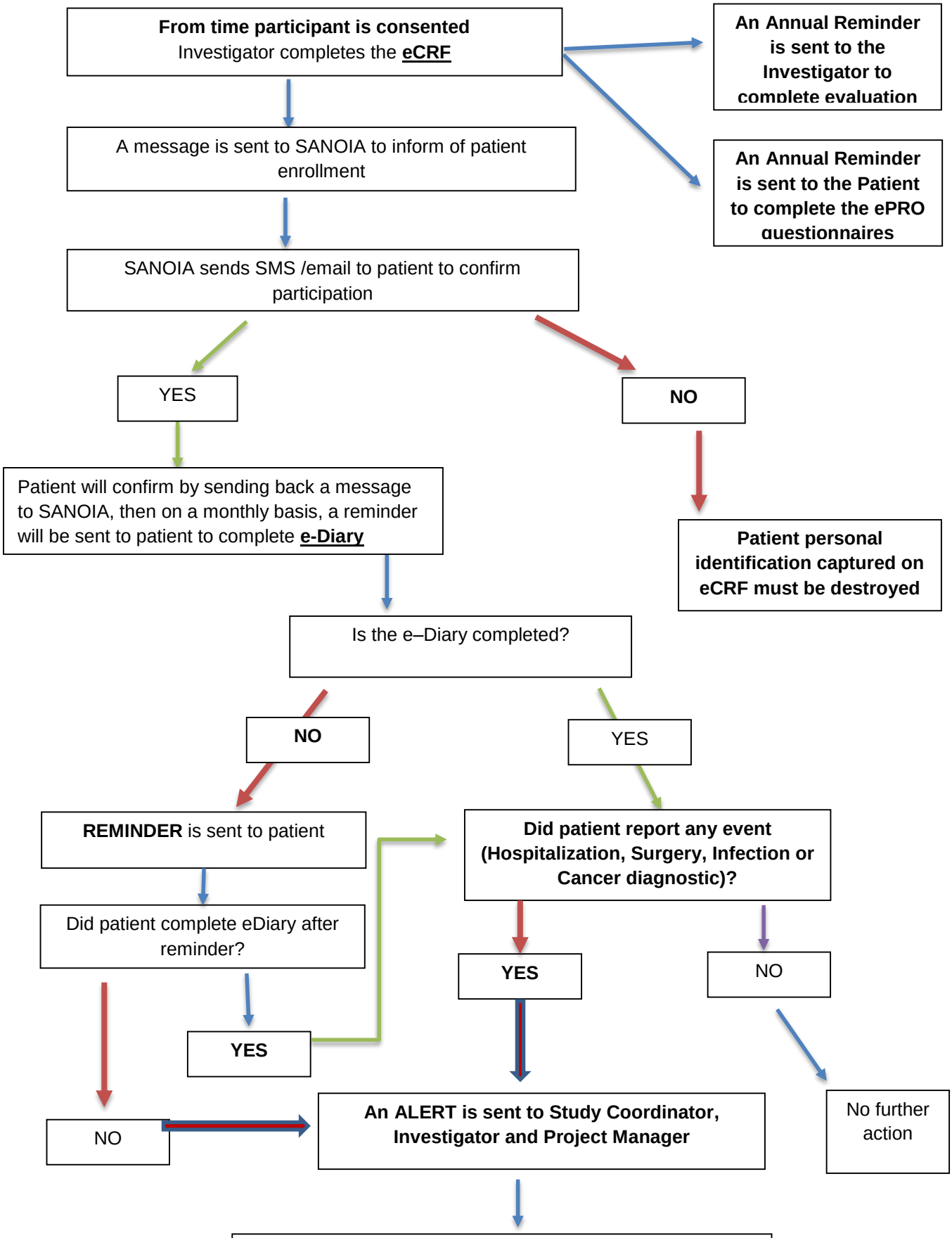
Patients

- Patient will complete the e-Diary on a monthly basis and the ePRO once a year
- Report all hospitalization, surgery and cancer diagnosis
- Obtain all hospitalization and surgery summary, as well as pathology reports from treating physicians and provide to Study Coordinators for upload on the secure server.
- Provide contact information for Study Coordinator to collect the documents necessary for the analysis.

STUDY SCHEDULE

	Inclusion	Study					
Date	**D0**	**M1**	**M2**	**…. Q 1 M until M36**	**M12 FU**	**M24 FU**	**M36 FU**
Investigators							
Clinical visit + physical examination	+						
Informed consent	+						
Inclusion and exclusion criteria assessment	+						
Enrollment	+						
Confirm Treatment	+				+	+	+
Disease activity assessment	+				+	+	+
IBD Disability Index	+				+	+	+
Validate Hospitalization and Cancer Diagnostic					+	+	+
Study Coordinators							
Confirm data entry by patient is complete		+	+	+	+	+	+
Upload Hospitalization summary and/ or Pathology reports		+	+	+	+	+	+
Follow up with patient if missing data		+	+	+	+	+	+
Patients							
Confirm Participation	+						
Complete e-Diary (monthly)		+	+	+	+	+	+
Complete annual e-PRO: SHS-VAS, FACIT-F, WPAI, Disability Index	+				+	+	+
Report Cancer diagnostic		+	+	+	+	+	+
Report Hospitalization		+	+	+	+	+	+
Obtain Hospitalization , surgery summary, pathology report if possible and provide to SC		+	+	+	+	+	+

STUDY PROCESS FLOW



STUDY LOGISTIC ARCHITECTURE

Internet site, data recording and management

- A dedicated Internet site will be built by SANOIA, a service provider with experience in patient e-Diary and e-PRO (Patient Reported Outcomes) to capture the information coming from the patients. SANOIA will also ensure adequate reminder SMS to be send to the patients for timely completion of the e-Diary and e-PRO. An alert system will be set up to inform Study Coordinators and Project Managers of incomplete data or report of Hospitalization, Surgery, Infection or Cancer diagnostic to allow timely tracking of the pertinent documents to upload on the Web Portal.

- A second Platform will be built by Telemedicine, (a Getaid service provider with experience in designing and managing eCRF), to house the Investigators database and eCRF pages that Investigators are required to complete.

- An interface (bridge) will be built between the two systems to allow :
  - Enrolled patients to be contacted to confirm their registration on their own smart phone/ computer after the Investigators completed their contact information on the eCRF
  - Investigators to have a summary of data entered by their patients for validation
  - Study Coordinators to receive alerts and update on their Dashboard
  - Update of Nat Coord and Project Managers Dashboard

- National Coordinators, Study Coordinators and Project Manager will each have their specific Dashboard for follow up on their respective data with a limited access for some.
  - National Coordinators Dashboard will show enrolment and project status in their country.
  - Study Coordinators Dashboard will show alerts regarding missing data or special events from patients in their own country or from the sites they manage.
  - Investigators Dashboard will show data from their own patients only.

- There will be a local language version of the documents provided to the patients (including electronic versions of information forms) for all the ECCO participating countries. I-CARE National Coordinators (two per participating country) will be responsible for translation of all documents
- Data will be entered directly on the site by gastroenterologist investigators and patients, and study coordinators will be able to upload pertinent documents.
- The gastroenterologist investigator will have access to the eCRF to complete enrollment information, including disease characteristics and demographic data, as well as the yearly summary.
- The patient will have a specific access to his e-Diary in local language
- All data will be stored on a dedicated server with a high security standard
- Data management and analysis will be under the responsibility of a Methodology Executive Coordinator, assisted by a General Methodology Consultant

E-CRF: CLINICAL DATA RECORDED AT INCLUSION

<u>Demographic and disease characteristic data, completed by the Investigator</u>

- Date of birth
- Gender
- Smoking status (current use, former use, never smoked)
- Alcohol consumption (< or >=30 g/day for men, < or >20 g/day for women)
- IBD subtype: CD/UC
- year of diagnosis
- disease duration at inclusion in I-CARE
- Montreal classification at diagnosis: A/L/B/p E
- Montreal classification at worst stage: A/L/B/p E
  - *for the colonic location, cumulative estimated microscopic and/or microscopic extent < or > 50% of the surface of colonic mucosa)*
- Associated Primary Sclerosing Cholangitis

History of cancer:

- Family history of lymphoma in a first-degree relative

- Family history of colorectal cancer in a first-degree relative
- Personal history of any type of cancer or high-grade dysplasia (organ, year of diagnosis, histological type)

Vaccination and infection history

- Previous vaccination against HPV (yes, no, date)
- Previous vaccination against HBV (yes, no, date)
- Previous vaccination against pneumococcus disease (yes, no, date)
- Personal history of symptomatic mononucleosis

Previous medications:

- Any oral form of 5-ASA
- Any form of systemic (oral or i.v.) corticosteroids, budesonide, budesonide MMX
- Thiopurines (azathioprine or 6-mercaptopurine)
- Methotrexate
- Infliximab: infliximab originator (Remicade), infliximab biosimilars (Inflectra, Remsima), other infliximab biosimilars
- Adalimumab: adalimumab originator (Humira), adalimumab biosimilars
- Certolizumab pegol
- Golimumab
- Vedolizumab
- Other medications related to IBD (natalizumab, cyclosporine, tacrolimus, mycophenolate mofetil, etc)

<u>For all of these preceding drugs</u>:

Previously/Currently/Never taken

For all drugs ever taken:

- *Date of first use*
- *If not currently taken, date of last use*
- *If currently taken, date of starting of the last continuous use (WA)*
- *Current daily dose (WA)*

Biological data (+ date of blood test)

- EBV serology (IgG pos or neg)
- HBV serology(surface antigen pos or neg; surface antibodies pos or neg)

- HCV serology (PCR pos or IgG neg)
- VZV serology (IgG pos or neg)
- HIV serology (IgG pos or neg)

Previous Surgery (month and year)

- Proximal small bowel resection
- Ileocaecal or ileal resection
- Stricturoplasty(ies)
- Segmental colectomy (ascending, transverse, descending, sigmoid, rectum)
- Subtotal colectomy with ileorectal anastomosis
- Total proctocolectomy with ileoanal anastomosis
- Surgical drainage of abdominal abscess
- Stoma (permanent or temporary) (ileostomy/colostomy)
- Perianal surgery (yes / no)

CLINICAL DATA RECORDED DURING FOLLOW UP

Patients will complete every month an e-Diary containing the following clinical elements:

- Disease score activity: HBI for CD and Walmsley (SSCAI) for UC
- CD-related perianal and enterocutaneous fistulas (data collected: active fistula draining or not)
- All IBD or non IBD related hospitalizations (date of event, and summary report); *patients will be encouraged to collect all their hospitalization and surgery reports and provide them to the Study Coordinator for upload.*
- All IBD or non IBD related surgeries (date of event)
- All endoscopies (date of endoscopic procedure): endoscopic disease activity will be classified as quiescent, mild/moderate, or severe by the gastroenterologist investigator based on the endoscopy report.
- All imaging studies (date of imaging studies): imaging disease activity will be classified as quiescent, mild/moderate, or severe by the gastroenterologist investigator.
- Any high-grade dysplasia or cancer as indicated in the e-Diary

- Any change (type and dose) among all medications recorded at inclusion (see above "previous medications")
- Any infectious events as indicated in the e-diary
- Participation of the included patient in any support program
- Inclusion in a clinical trial. If patient is enrolled in a blinded Randomized Clinical Trial, patient does not need to withdraw from I-CARE, provided that follow up information can be obtained on trial medication when the blind is lifted.
- smoking status

For IBD patients starting new approved drugs during follow-up and those switching from anti-TNF therapy to the new approved drug, efficacy and safety will be collected.

Patients will also complete on a yearly basis an e-PRO containing the following questionnaires:

- The SHS-IBD VAS questionnaire
- The FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue) questionnaire
- The WPAI (Work Productivity and Activity Impairment) questionnaire
- The IBD Disability Index questionnaire

The gastroenterologist will complete at least once yearly the annual summary of Infections, malignancy or pre-malignancy, and hospitalizations, related or not to the Inflammatory bowel disease (flare, complications, infection or surgery). He will also assess the Clinical Disease Activity Index, using endoscopy or radiology as available, and validate all events that have been reported by the patients.

PROJECT MANAGEMENT

The GETAID is the sponsor of the I-CARE study. Various group are involved in the conduct of the study and their responsibilities are listed below:

Executive Committee: The executive committee is in charge of the initial construction of the scientific content and logistic architecture of the project, organisation and project oversight. Members include:

- Laurent Peyrin-Biroulet, (GETAID)- President

- Laurent Beaugerie, (SNFGE)- President of Scientific Committee
- Jean François Rahier, (BIRD)- Director of Infections Committee
- Filip Baert, (ECCO/BIRD)- General Secretary
- Marie Jo Bertin, (GETAID)- Project Director

Scientific Committee: The scientific committee (at least 2 meetings per year) will decide and control all aspects of the scientific content and production of initial and secondary nested projects, and the relationship with scientific organizations, Drug Agencies, and Patients Associations. The scientific committee consists of:

- Executive Committee
- Cancer Committee
- Infections Committee
- National Coordinators
- EFCCA (1 representative)
- ECCO representatives

Dissemination, Exploitation and Communication of the project:

- ECCO, Severine Vermeire, President
- National Coordinators (2 x participating country)
    - Recruitment, supervision and motivation of Investigators in the participating countries
    - Recruitment of Study Coordinators according to the expected number of patients in their country (1 SC/1000 patients)
    - Translations, document collection, ICF generation /review
    - Regulatory & EC/IRB as well as Safety Submission in their own country

- EFCCA
    - Raise public and scientific awareness of the project and inflammatory bowel disease therapies,
    - Facilitate networking and mutual communication both to scientific community and general public,
    - Identify target groups and reach all potential scientific and non-scientific audiences,
    - Ensure most efficient exploitation of project results

Operations Management

Project Manager, Christine Nguyên Demange (GETAID): Responsible for daily operations and interaction with Nat Coordinators and Study Coordinators

Project Director, MJ Bertin (GETAID): Responsible for the overall clinical operations and overview of the project, manage contracts and budget.

Study Coordinators, at National Level:

- Under the administrative and legal responsibility of the National Coordinators
- Sites management in their country (interaction with Investigators and Patients)
- Monitoring data, uploading hospitalisations and pathology reports on the portal.
- Reporting to the project manager for project related issues.

EDC and Data Management:

- Telemedicine will be responsible for providing the Investigators data collection platform and eCRF while SANOIA is responsible for the secure e-Diary and ePRO. GETAID will be responsible for data management.

Pharmacovigilance:

- GETAID: Data base Setup, AE/SAE Reconciliation/ periodic listing
- National Coordinators: Annual safety reports processing & reporting SAE to Regulatory Authorities for their own country.

Methodologists:

- F Carrat, Institut Pierre Louis d'Épidémiologie et de Santé Publique, UMR-S 1136 F-75012 (consultant Methodologist)
- Raphael Porcher, METHODS team : Méthodes de l'évaluation thérapeutique des maladies chroniques Inserm Sorbonne Paris Cité – U1153, and
- Cédric Baumann, Methodological and Biostatistical Support Unit - ESPRI, Nancy University Hospital, will be responsible for overall statistical analysis plan, analysis variables, sample calculation, analysis set, statistical method and report.

Cancer Committee: Coordinator: Laurent Beaugerie. Members of the Cancer committee will assess all reported cases of Cancer and evaluate their relationship with the treatments.

Infection Committee: Coordinator: Jean François Rahier. Review and Adjudication of all reported hospitalisation. Determine reportable Drug Reaction and the relationship of Infection in regards to treatment.

Disease burden (PROs) and natural history: Coordinator: Laurent Peyrin-Biroulet.

Risk-benefit ratio and health care costs: Coordinator: Filip Baert

STATISTICAL ANALYSIS

Risk of lymphoma in patients exposed to anti-TNF (main element of primary objective)

To assess the role of anti-TNF exposure status at lymphoma diagnosis on the risk of lymphoma, we will use a stratified on propensity score method. The propensity score, i.e. the probability of being treated with anti-TNF in view of the observed covariates, will be calculated with a logistic regression model for each subject. The propensity score for receiving anti-TNF will be the predicted probability obtained from the logistic equation given the covariate values. We will use stratified Cox regression models to quantify the strength of associations between anti-TNF exposure and time to lymphoma diagnosis. In these models, anti-TNF exposure will be introduced as a time-dependent covariate and strata will be based on the propensity score quintiles as defined above. For the multivariable Cox model, we will use forced-entry methods to include age and sex, while other potential confounders will be tested separately in a univariate Cox regression model and potentially included in the multivariate analysis based on a P-value <0.25. Note that the small expected number of lymphomas will prevent us from including more than four or five covariates in the final multivariate model.

Other analyses (other elements of the main objective and secondary objectives)

Statistical analyses related to the secondary elements of the main objective and all the elements of the secondary objectives will be specifically designed by the I-CARE methodologists, adapting

the choice of the methods to the frequency of the events of interest, and the choice of the covariates to the established or suspected confounders. Maximal adjustment extent (adjustments for patient characteristics, IBD phenotype/activity and propensity to use any drug) will be required for testing the independent potential chemo preventive effects of 5-amino-salicylates, thiopurines and anti-TNF, on the risk of colorectal cancer.

EXPECTED RESULTS

I-CARE is the first observational European prospective cohort study that will provide unique information (safety, efficacy/potential for disease modification, risk-benefit ratio, and healthcare costs) on the long-term use of anti-TNF therapy in IBD, using a predefined standardized follow-up. These real world data will be used to guide clinicians as well as Healthcare authorities to provide the best care for IBD patients by optimizing available therapies. These findings may assist in maximizing benefits and minimizing risks among IBD patients who are candidates for anti-TNF therapy. This is why I-CARE is considered a high-priority project by European organizations working in the field of Gastroenterology and IBD (EFCCA, ECCO, and the GETAID).

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